This document contains the Human Stem Cell Research Advisory Committee's recommended *Guidelines for Human Stem Cell Research* developed pursuant to Health and Safety Code §125118.

Additional supporting information may be found at http://www.mch.dhs.ca.gov/

RECOMMENDED GUIDELINES FOR HUMAN STEM CELL RESEARCH PURSUANT TO HEALTH AND SAFETY CODE §125118

§1 Scope of the Guidelines

These guidelines are proposed pursuant to Health and Safety Code §125118. They apply to all individuals and institutions performing human stem cell research in California by deriving or using covered stem lines, defined in Section 2 below, or cells from those covered stem lines, except research funded by the California Institute for Regenerative Medicine (CIRM) to the extent it is exempted by the terms of Proposition 71 from other State law.

§2 Definitions

As used in these guidelines:

(a) "Acceptably derived" means derived in accordance with the requirements of these guidelines.

(b) "Clinical trial" means a scientifically designed and executed investigation of a medical intervention in humans that is aimed at determining the safety, efficacy, and pharmacological effects (including toxicity, side effects, incompatibilities, and interactions), of the intervention. These include Phase I, II, and III clinical trials under the Food and Drug Administration (FDA) regulations.

(c) "Covered cells" mean cells from covered stem cell lines or cells differentiated from cells that are from covered stem cell lines.

(d) “Covered research” means research that derives a covered stem cell line or that uses covered cells.

(e) “Covered stem cell line” means a culture-derived, human pluripotent stem cell population that is capable of: 1) sustained propagation in culture; and (2) self-renewal to produce daughter cells with equivalent developmental potential. This definition includes both embryonic and non-embryonic human stem cell lines regardless of the tissue of origin. “Pluripotent” means capable of differentiation into mesoderm, ectoderm, and endoderm.

(f) “First-in-human trials” means the first time that particular kinds of cells are being transplanted into humans for particular diseases or in particular organ systems.

(g) “Human subject” means a living individual about whom an investigator (whether professional or student) conducting research obtains:

(1) Data through intervention or interaction with the individual; or

(2) Identifiable private information.

(h) “Institutional field strength” means the skill and experience of the team that is proposing to undertake an innovative procedure on a patient at an institution.

(i) “Institution” means any public or private entity or agency (including federal, state, local or other agencies).

(j) “Institutional Review Board” (“IRB”) is an entity established in accordance with Title 45, Code of Federal Regulations, Section 46.107.

(k) “Permissible expenses” means necessary and reasonable costs directly incurred as a result of donation or participation in research activities. Permissible expenses may include, but are not limited to, costs associated with travel, housing, child care,

medical care, health insurance and actual lost wages.

(l) "Research" means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of these regulations, whether or not they are conducted or supported under a program which is considered research for other purposes.

(m) "Somatic cell nuclear transfer" (SCNT) means the transfer of a somatic cell nucleus into an oocyte.

(n) "Stem Cell Research Oversight Committee" (SCRO Committee) means a committee established in accordance with Section 4 below.

§3 Activities Not Permitted

The following activities are not permitted in California.

(a) Human reproductive cloning, as defined in California Health and Safety Code Section 125292.10. subdivision (k), or reproductive uses of SCNT prohibited by article XXXV Section 3 of the California Constitution.

(b) The culture in vitro of (i) any intact human embryo or (ii) any product of SCNT, parthenogenesis or androgenesis, after the appearance of the primitive streak or after 12 days, whichever is earlier. The 12 day prohibition does not include any time during which the embryos or cells have been stored frozen.

(c) The introduction of stem cells from a covered stem cell line into nonhuman primate embryos.

(d) The introduction of any stem cells, whether human or nonhuman, into human embryos.

(e) Breeding any animal into which stem cells from a covered stem cell line have been introduced.

§4 SCRO Committee Membership and Function

(a) A SCRO Committee shall comprise persons with expertise in, including but not limited to, developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research. A SCRO Committee shall include at least one non-scientist member of the public who is not employed by, or appointed to, or remunerated by the relevant research institution, and who is not part of the immediate family of a person who is affiliated with the institution. In addition, a SCRO Committee shall include at least one patient advocate. Any member of a SCRO Committee may be reimbursed for reasonable out-of-pocket expenses for attending the meeting, not including lost wages. No SCRO Committee may have a member participate in the SCRO Committee's initial or continuing review of any project in which the member has a conflict of interest, except to provide information to the SCRO Committee.

(b) The designated SCRO Committee shall provide scientific and ethical review of covered research consistent with the requirements of these guidelines.

(c) The SCRO Committee shall facilitate the education of investigators about these guidelines.

(d) A SCRO Committee may provide oversight for two or more funded research institutions, provided the SCRO Committee has oversight authority consistent with the requirements of these guidelines.

(e) A SCRO Committee may be convened by an institution, a group of institutions, or a

State agency.

§5 SCRO Committee Review and Notification

(a) Covered research involving the procurement or use of human oocytes as part of covered research may not commence without SCRO Committee review and approval in writing. For such SCRO Committee review and approval, a member of the Committee with expertise in assisted reproduction shall be present. The designated SCRO Committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (a)(3) of this guideline as a condition of granting its approval. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to use oocytes, including a justification for the number needed. If SCNT is proposed, a justification for SCNT shall be provided.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Animal Care and Use Committee (IACUC), Institutional Bioethics Committee (IBC), or other mandated review.

(4) Further requirements for research involving the procurement or use of human oocytes are provided in Section 8 below.

(b) Covered research involving use of human embryos may not commence without SCRO Committee review and approval in writing. The designated SCRO

Committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (b)(3) of this section as a condition of granting its approval. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to use embryos, including a justification for the number needed.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(c) Covered research with the aim to derive or create a covered stem cell line may not commence without SCRO Committee review and approval in writing. The designated SCRO Committee may require that modification be made to proposed research, or documentation of compliance with the requirements of subdivision (c)(4) of this section as a condition of granting its approval. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to derive a covered stem cell line.

(2) If SCNT is proposed as a route to generating human stem cell lines, a justification for SCNT shall be provided.

(3) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(4) Provide documentation of compliance with any required review of the

proposed research by an IRB, IBC, or other mandated review.

(5) Document how stem cell lines will be characterized, validated, stored, and distributed to ensure that the privacy of the donor is protected and the confidentiality of identifiable information is maintained.

(6) Further requirements for research involving the derivation or creation of covered stem lines are provided in Section 7 below.

(d) Covered research constituting clinical trials involving the use of covered cells may not commence without SCRO Committee review and approval in writing. In addition, clinical trials involving the transfer of non-autologous neural-progenitor stem cells to a human central nervous system shall also receive SCRO Committee review and approval before commencement. The SCRO Committee shall ensure that adequate scientific and ethical review of each protocol has taken place. The SCRO Committee may require that modification be made to proposed research, or documentation of compliance with (d)(4) of this section as a condition of granting its approval. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for introducing stem cells into humans.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human tissues.

(4) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(5) Further requirements for research involving the derivation or creation of covered stem lines are provided in Section 7 below.

(e) Purely in vitro covered research may not commence without written notification to the designated SCRO Committee. At a minimum, the notification shall:

(1) Provide assurance that all covered stem cell lines have been acceptably derived.

(2) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(f) Covered research introducing cells from or differentiated from covered stem cell lines into non-human animals, or introducing neural-progenitor cells into the brain of non-human animals at any state of embryonic, fetal, or postnatal development may not commence without SCRO Committee review and approval in writing. The designated SCRO Committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (f)(4) of this section as a condition of granting its approval. The SCRO Committee may establish guidelines and procedures for expedited review of animal research so that review by the entire SCRO Committee is not required. At a minimum, the SCRO Committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for introducing stem cells into non-human animals.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of

the human cells into the nonhuman animal tissues.

(4) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(g) In cases where SCRO Committee approval is required, a SCRO Committee shall notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure SCRO Committee approval of the research activity. If the SCRO Committee decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(h) SCRO Committee approvals shall be reviewed no less frequently than once per year. The renewal review shall confirm compliance with all applicable rules and regulations. A SCRO Committee may revoke its prior approval of research under this section, and require modifications to the plan or design of a continuing research project before permitting the research to continue. The SCRO Committee may establish guidelines and procedures for expedited review of renewals so that review by the entire SCRO Committee is not required.

§6 Acceptable Research Materials

All cells from or differentiated from covered stem cell lines used in covered research must be "acceptably derived." To be "acceptably derived," the stem cell line must:

(a) Have been approved by the National Institutes of Health, or

(b) Been deposited in the United Kingdom Stem Cell Bank, or

(c) Been derived by, or approved for use by, a licensee of the United Kingdom Human Fertilization and Embryology Authority, or

(d) Been derived in accordance with the Canadian Institutes of Health Research Guidelines for Human Pluripotent Stem Cell Research under an application approved by the National Stem Cell Oversight Committee, or

(e) Have been derived under the following conditions:

(1) Donors of gametes, embryos, somatic cells or human tissue gave voluntary and informed consent.

(2) Donors of gametes, embryos, somatic cells or human tissue did not receive valuable consideration. This provision does not prohibit reimbursement for permissible expenses as determined by an IRB.

(3) A person may not knowingly, for valuable consideration, purchase or sell gametes, embryos, somatic cells, or human tissue for research purposes. This provision does not prohibit reimbursement for permissible expenditures as approved by a SCRO Committee or IRB, or permissible expenses as determined by an IRB. "Permissible expenditures" include reasonable payment for the removal, processing, disposal, preservation, quality control, transportation of materials, and storage of oocytes or embryos necessary, and reasonable costs directly incurred as a result of persons, not including human subjects or donors, providing gametes, embryos, somatic cells, or human tissue for research purposes.

(4) Donation of gametes, embryos, somatic cells or human tissue was overseen by an IRB (or, in the case of foreign sources, an IRB-equivalent).

(5) Individuals who consented to donate stored gametes, embryos, somatic cells or human tissue were not reimbursed for the cost of storage prior to the

decision to donate.

§7 Additional Requirements for Covered Research Deriving New Human Stem Cell Lines

When reviewing proposals to derive new human stem cell lines, the SCRO Committee must confirm that donors of gametes, embryos, somatic cells or human tissue have given voluntary and informed consent.

§8 Additional Requirements for Covered Research Involving Oocytes

Assisted oocyte production and alternate methods of oocyte retrieval conducted for research purposes in California after January 1, 2007, are subject to the detailed provisions of California Health and Safety Code Sections 125330 through 125355, which should also be consulted. This section of the guidelines includes provisions taken from those Code Sections, which do not apply to CIRM-funded research, as well as provisions from the CIRM regulations.

(a) When human oocytes are required for covered research, the SCRO Committee must confirm the following conditions were or will be met in connection with the oocyte retrieval, whether or not the oocyte retrieval takes place within California:

(1) The clinic performing oocyte retrieval is a member of the Society for Assisted Reproductive Technology.

(2) The IRB that approved donation of the oocytes found that risks are reasonable even if there is no anticipated benefit to the donor.

(3) Before giving her informed consent, the donor was provided with a standardized medically accurate written summary of health and consumer issues as provided by Section 125335.

(4) The donor gave written and oral informed consent to the oocyte retrieval procedure consistent with Section 125340 and:

A. The description of foreseeable risks of the procedure included information regarding the risks of ovarian hyperstimulation syndrome, bleeding, infection, anesthesia and pregnancy.

B. The physician disclosed his or her relationship to the research or researcher(s) to the oocyte donor.

C. The donor was informed of her option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the donor shall be informed of her right to determine the method of recontact. The donor must be informed that she has the option to initiate recontact. The investigators shall not initiate recontact unless the donor has consented, and this consent is documented in the research record.

D. The researcher has ascertained that the donor has understood the essential aspects of the research, following a process approved by the designated IRB or SCRO Committee. Understanding the essential aspects of the research includes understanding at least that:

(i) Her oocytes will not be used for reproductive purposes.

(ii) There are medical risks in oocyte retrieval, including the risks of ovarian hyperstimulation syndrome, bleeding, infection, anesthesia, and pregnancy.

(iii) The research is not intended to benefit her or any other individuals

directly at this time.

(iv) Stem cell lines may be derived from her oocytes through fertilization, SCNT, parthenogenesis, or some other method.

(v) Stem cell lines developed from her oocytes will be grown in the lab and shared with other researchers for studies in the future.

(vi) If stem cells are to be transplanted into patients, researchers might recontact the donor to get additional health information.

(vii) Donors receive no payment beyond reimbursement for permissible expenses.

(viii) Stem cell lines derived as a result of her oocyte donation may be patented or commercialized, but the donor will not share in patent rights or in any revenue or profit from the patents.

(5) That the donor received an objective and accurate statement about the existing state of the research for which the donor is providing oocytes.

(6) That all donors prior to the oocyte retrieval procedure received psychological and physical screening in accordance with the appropriate standard of care.

(7) That each donor was given a postprocedure medical examination at a time within the standard of care to determine if she experienced an adverse health effect that was a result of the procedure. The donor shall be informed that she has the right to a second opinion if she has any medical concerns.

(8) That the donor has access to and coverage for medically appropriate medical care that is required as a direct result of the procedure for research purposes. The research program or project shall ensure that payment or coverage of

resulting medical expenses be provided at no cost to the donor and that a summary of the arrangements the procuring entity has made for coverage or payment for medical care related to the oocyte retrieval was provided to the donor prior to the procedure.

(9) That the donor received a summary informing the subject that oocytes may not be sold or transferred for valuable consideration except as set forth in Section 125350.

(10) That the donor received a disclosure if the physician and surgeon and his or her immediate family members had any professional interest in the outcome of the research or of the oocyte retrieval procedure and, if so, that the donor received disclosure that he or she carries the interest of both the subject and the success of the research.

(11) That written records were established and maintained as part of the oocyte procurement process that comply with Section 125342.

(12) That no employee who works in the unit conducting stem cell research using human oocytes is a subject in the project. This includes the principal investigator or key personnel of the project and the persons who report to or are supervised by them, and the immediate family members of any of the above persons.

(13) That the physician and surgeon performing the oocyte retrieval procedure did not have a financial interest in the outcome of the research.

(14) That donors have been offered an opportunity to document their preferences regarding future uses of their donated materials and that the consent process

fully explored whether donors have objections to any specific forms of research to ensure that their wishes are honored.

(b) The physician attending to any donor and the principal investigator shall not be the same person unless exceptional circumstances exist and an IRB has approved an exemption from this requirement.

(c) The procurement and disposition for research purposes of oocytes initially provided for reproductive uses, either for use by the donor or another woman, shall not knowingly compromise the optimal reproductive success of the woman in infertility treatment. Pursuant to this requirement, the SCRO Committee shall confirm the following:

(1) The infertility treatment protocol is established prior to requesting or obtaining consent for a donation for research purposes and that the prospect of donation for research does not alter the timing, method, or procedures selected for clinical care.

(2) The woman in infertility treatment makes the determination that she does not want or need the oocytes for her own reproductive success.

(3) The donation of oocytes for research is done without valuable consideration either directly or indirectly.

(4) If the procurement of oocytes involves a donor providing oocytes for another woman's reproductive use, then the donation to research must be expressly permitted by the original donor.

(5) If the procurement of oocytes involves use of materials donated for reproductive use by another woman and with valuable consideration in excess

of reimbursement for permissible expenses for the oocyte donor, then oocytes may not be used for covered research.

(d) Oocytes for research that were retrieved before January 1, 2007, need not meet the requirements of subsection (a) above if the oocytes were donated pursuant to protocols or standards that are generally recognized and accepted by national or international scientific bodies.

(e) No human oocyte shall be acquired, sold, offered for sale, received, or otherwise transferred for valuable consideration for the purposes of medical research or development of medical therapies. For purposes of this section, "valuable consideration" does not include reasonable payment for the removal, processing, disposal, preservation, quality control, and storage of oocytes or embryos.

(f) No payment in excess of the amount of reimbursement of direct expenses incurred as a result of the procedure shall be made to any subject to encourage her to produce human oocytes for the purposes of medical research.

§9 Additional Requirements for Covered Research Involving Clinical Trials

(a) When reviewing clinical trials with covered cell lines or cells, the SCRO Committee shall require the investigator to:

(1) Establish that there is sufficient institutional field strength to justify conducting such research, particularly with respect to first-in-human trials. This should include a team with experts in the relevant sciences (including biostatistics) and all relevant clinical and surgical areas as well as psychological support. In addition, there must be sufficient regulation and oversight at the institution to undertake innovative clinical trials. The goal is

to reduce the probability that failure will be a function of the skills of the relevant team and to reduce probability of harm to subjects.

(2) Establish that there is sufficient knowledge of the risks and benefits associated with the proposed intervention that it is reasonable to proceed in human populations.

(3) Provide justification that the risks of the trial have been minimized and are reasonable in relation to the anticipated benefits of the trial, including benefits from the generalizable knowledge to be gained.

(4) Address the issue of the diversity of the research subject population, including a justification if under-represented groups (women, minorities, children) are not included.

(5) Register the clinical trial with a public clinical trials registry, such as the National Institute of Health's ClinicalTrials.gov.

(b) The SCRO Committee may require, for safety reasons, the testing or screening of donors of the biological materials used to produce the covered cells prior to its commencement.

(c) All clinical trials involving the use of covered cells shall also be reviewed and approved by an IRB before commencement.

(1) IRBs shall require that informed consent for any clinical trials involving covered stem cells and their derivatives include information about the biological source of the material and how they were produced.

(2) IRBs shall ensure that the language used in informed consent for clinical trials that involve covered cells does not convey an unrealistic impression of the

direct benefit of trial participation. For example, it would be inappropriate to describe early phase research as “stem cell therapy,” or “therapeutic cloning”, or “gene therapy,” because of the potential misleading connotations of the words “therapy” or “therapeutic”.

(3) IRBs shall require that any clinical trials involving covered stem cells and their derivatives shall have an adequate Data Safety Monitoring Board established to periodically review outcomes and safety of the trial and provide a monitoring plan for the trial.

(4) In evaluating clinical trials, IRBs shall consider implications of the trial for the descendants of the trial subjects, for example, in research that includes germ line modification.

(d) Institutions conducting clinical trials are encouraged to develop methods that allow SCRO Committees and IRBs to work together to discharge these responsibilities efficiently, while bringing needed expertise in stem cell science to bear on oversight of such trials.

§10 Informed Consent Requirements

(a) All covered human subjects research shall be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005, and California Health and Safety Code Section 24173. In accordance with existing law, California Health and Safety Code Section 24173 does not apply to a person who is conducting research as an investigator within an institution that holds an assurance with the United States Department of Health and Human Services pursuant to Title 45 Code of Federal Regulations Part 46, revised June 23,

2005, and who obtains informed consent in the method and manner required by those regulations.

(b) In addition to any other statutory requirements or sections of these guidelines, the following provisions shall apply when covered research involves donation of gametes, embryos, somatic cells or human tissue, or derivation of new covered stem cell lines, which donation or derivation occurs after the effective date of these guidelines:

(1) Research may not be performed that violates the documented preferences of donors with regard to the use of their donated materials. The SCRO Committee or IRB must confirm that donors of gametes, embryos, somatic cells or human tissue to be used to derive stem cell lines have given voluntary and informed consent in accordance with this Section. To ensure donors are fully informed of the potential uses of donated materials, researchers shall disclose, in addition to the general requirements for obtaining informed consent identified in subdivision (a) of Section 10, all of the following, unless a specific item has been determined by the SCRO Committee or IRB to be inapplicable:

A. Derived cells or cell products may be kept for many years.

B. Whether the identity(ies) of the donor(s) will be ascertainable to those who work with the resulting cells or cell products. If the identity(ies) of the donor(s) are retained (even coded), researchers must discuss any plans for recontact of donors of materials used to derive cell lines and obtain consent for recontact. This requirement includes both

recontacting donors to provide information about research findings and to ask for additional health information. Recontact may only occur if the donor consents at the time of donation.

C. Researchers may use cell lines for future studies, some of which may not be predictable at this time.

D. Derived cells or cell products may be used in research involving genetic manipulation.

E. Derived cells or cell products may be transplanted into humans or animals.

F. Derived cells or cell products are not intended to provide direct medical benefit to the donor(s), except in the case of autologous donation.

G. The donation is being made without restriction regarding who may be the recipient of transplanted cells, except in the case of autologous donations.

H. That neither consenting nor refusing to donate materials for research will affect the quality of any future care provided to potential donors.

I. That the results of research may be patentable or have commercial potential, and that the donor will not receive patent rights and will not receive financial or any other benefits from future commercial development.

(2) Researchers shall offer donors an opportunity to document their preferences regarding future uses of their donated materials. Researchers may choose to use materials only from donors who agree to all future uses.

(3) For covered research involving the donation and destruction of embryos for stem cell research, the informed consent process shall include a statement that embryos will be destroyed in the process of deriving embryonic stem cells.

(4) For covered research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.

(5) For covered research involving the donation of somatic cells for SCNT, informed consent shall include a statement as to whether the donated cells may be available for autologous treatment in the future.

§11 Record Keeping and Reporting

(a) Each institution performing covered research shall maintain records documenting:

(1) Required review or notification requirements in these guidelines.

(2) Every gamete, somatic cell, embryo donation or product of SCNT that has been donated, created or used. This record should be sufficient to determine whether such materials comply with these guidelines and should document the final disposition of such materials.

(b) Such records shall be made available at the Department's request.

(c) Each SCRO Committee that has reviewed covered research shall report to the Department, annually, on the number of covered research projects that the SCRO Committee has reviewed, and the status and disposition of each of those projects, including any information collected pursuant to Section 125342 concerning oocyte retrieval.

(d) Each SCRO Committee shall also report to the Department regarding unanticipated problems, unforeseen issues, or serious continuing investigator noncompliance with

the requirements or determinations of the SCRO Committee with respect to the review of covered research projects, and the actions taken by the SCRO Committee to respond to these situations.